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Diffusion tensor magnetic resonance imaging tractography in cognitive disorders

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Purpose of review

The advent of novel techniques for tracing connections *in vivo,* such as diffusion tensor magnetic resonance imaging tractography, allows us, for the first time in the human brain, to study the microstructural integrity of white matter fibres and perform virtual dissections of large scale neurocognitive networks. This review will outline the advantages and limitations of applying diffusion tensor magnetic resonance imaging to the study of cognitive and behavioural disorders in neurology and psychiatry.

Recent findings

Diffusion tensor magnetic resonance imaging has been used to re-explore the anatomy of white matter tracts in the living human brain and to create connectional models of brain function. Beyond its application to classical disconnection syndromes, diffusion tensor magnetic resonance imaging is becoming an important tool to extend the disconnectionist paradigm to neurodevelopmental and neurodegenerative disorders.

Summary

For the first time, we are able to correlate disconnecting lesions with clinical symptoms *in vivo* and test the disconnection mechanism directly in cognitive disorders. With diffusion tensor magnetic resonance imaging tractography alone and in combination with other magnetic resonance imaging techniques, researchers are able to detect abnormalities in white matter that are not visible with conventional magnetic resonance imaging.

Keywords

cognitive disorders, diffusion tensor magnetic resonance imaging, disconnection syndromes, hodology, tractography, white matter tracts

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Abbreviations

DLB	dementia with Lewy bodies
DT-MRI	diffusion tensor magnetic resonance imaging
MCI	mild cognitive impairment
MRI	magnetic resonance imaging

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Introduction

> *Nothing defines the function of a neuron better than its connections*
>
> M.-M. Mesulam

The brain is organized in large-scale networks that are made up of long tracts connecting distant relay stations [1••]. These networks are important for the development of higher brain functions such as language, praxis, social behaviour and emotion. Lesions affecting white matter connections lead to dysfunction, and cognitive disorders are sometimes better explained by a disconnection mechanism between distant cerebral regions than by primary damage of those regions themselves. For a disconnectional approach to studying brain function and dysfunction, detailed knowledge of the anatomy of white matter connections is paramount.

Hodology is the science of connectional anatomy and, despite several decades of tracing studies in animals, our knowledge of human brain connections has progressed very little since the beginning of the last century [2•]. Fortunately, over the last 10 years, we have seen a spectacular development of magnetic resonance imaging (MRI) techniques for the study of connections in the living human brain. One technique for exploring white matter pathways *in vivo* is diffusion tensor MRI (DT-MRI) tractography [3,4]. Despite some limitations, DT-MRI tractography is a promising technique to explore the anatomical basis of human cognition and its disorders.

This review will outline some of the most recent developments of DT-MRI-tractography, and its application to cognitive disorders in neurology and psychiatry.

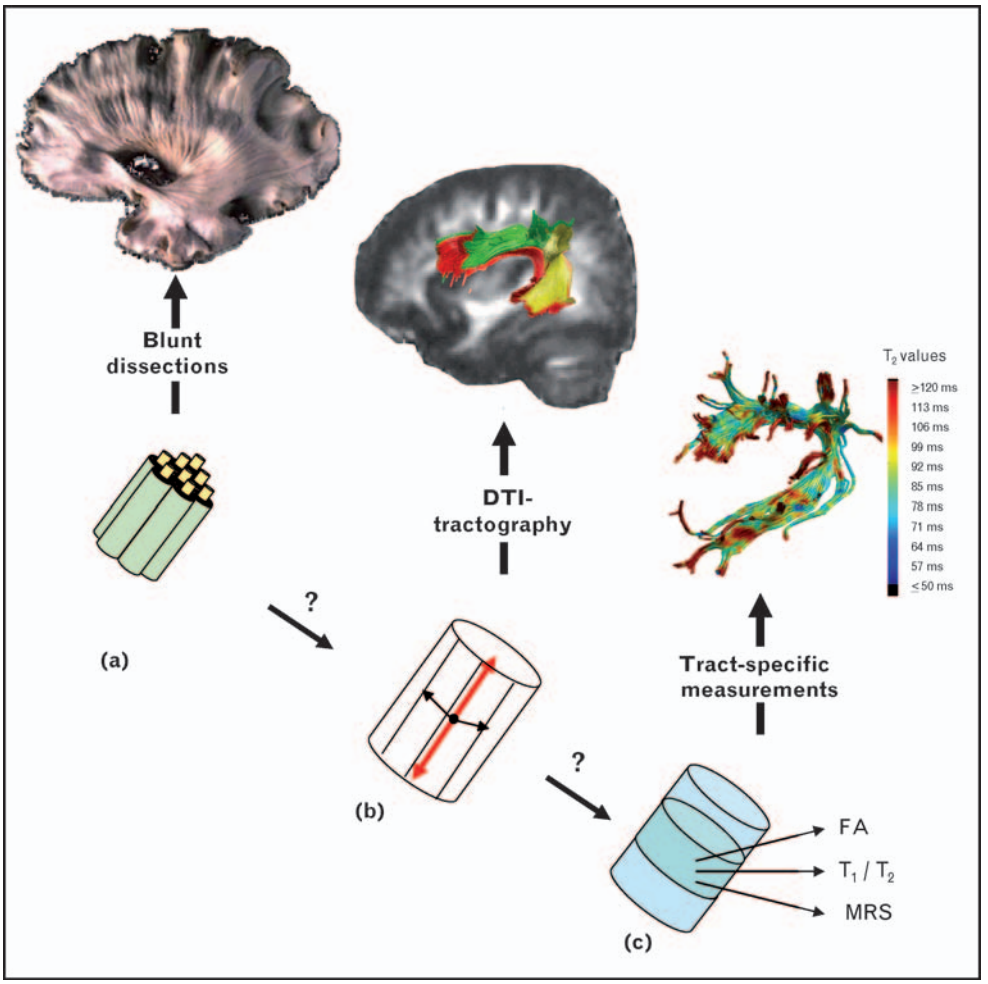
Towards in-vivo quantitative analysis of structural, metabolic and functional properties of white matter tracts

Until recently, the only way to identify white matter anatomy in humans was through the histological analysis of microstructural organization of fibres or post-mortem blunt dissections of large white matter tracts (Fig. 1a).

With DT-MRI tractography one can perform 'virtual dissections' of the living human brain and display connectional maps on a large scale that are faithful to the classical description of earlier neuroanatomists (Fig. 1b) [5,6]. DT-MRI tractography is a non-invasive technique that instead of visualizing axons directly, reconstructs their trajectories by measuring the diffusivity of water along different directions on a voxel-by-voxel basis [3,4]. The motion of water molecules is modified by local tissue components such as cell membranes and myelin. Within white matter the parallel orientation of axons constrains water molecules to move preferentially along the main direction of axons (a characteristic termed 'anisotropic diffusion'). Tractography algorithms aim to reconstruct the trajectories of white matter tracts by piecing together diffusion signals from contiguous voxels [3]. Tractography has been used to study white matter anatomy in healthy populations [5,6] and white matter changes in a wide range of conditions including congenital abnormalities of the corpus callosum and cerebellum [7], epilepsy [8•], early [9•] and late onset schizophrenia [10], and Alzheimer's disease [11,12].

Also, DT-MRI (i.e., not tractography *per se*) provides unique insights into the fine architecture of neuronal tissues and to changes associated with various physiopathological states [4]. For example fractional anisotropy, an index that quantifies the directionality of diffusion on a scale from zero (when diffusion is totally random) to one (when water molecules are able to diffuse along one direction only), has been shown to be highly sensitive to the wallerian degeneration of corticospinal tracts in stroke patients [13]. Several methods for the analysis of DT-MRI data have been used to identify between-group differences

Figure 1 Towards in-vivo quantitative analysis of structural properties of white matter tracts



(a) Myelinated axons group together to form discrete bundles. Parallel bundles form large white matter fasciculi that can be visualized post-mortem using blunt dissections. (b) Diffusion tensor magnetic resonance imaging (DT-MRI) tractography allows performance of 'virtual dissections' in the living human brain. DT-MRI signal reflects the orientation of fibres within a voxel. DT-MRI tractography algorithms reconstruct tracts by pieceing together DTI signals from contigous voxels. (c) The combination of DT-MRI tractography and other magnetic resonance imaging techniques allows the mapping of signal changes within specific tracts. The quantification of signal changes (e.g. fractional anisotropy, absolute T1and T2, magnetic resonance spectroscopy metabolites) can be used to detect the microstructural and metabolic properties of fibres within a single white matter tract.

Table 1 Methods of analysis used for diffusion tensor magnetic resonance imaging data

Data-led analysis	Hypothesis-led analysis
Whole-brain voxel-based analysis (VBA) This is an operator-independent approach that allows the analysis of the entire brain volumes without a-priori hypothesis regarding the anatomical location of between-group differences. This can be very useful as exploratory analysis especially where white matter changes are diffuse. Adapting the VBA approach, developed for functional and structural imaging data, to DT-MRI data, however, is not necessarily straightforward [14]. Coregistration of low resolution, high contrast fractional anisotropy maps may generate significant misregistration and partial volume artefacts in regions of high and low anisotropy (e.g. around the ventricles). Also the accurate localization of differences to specific tracts is difficult as data are often heavily smoothed as part of the pre-processing. This results in low resolution parametric maps from which to infer group differences [15•]. Anatomical identification of regions exhibiting significant group differences can be difficult as clusters of voxels will not typically lie neatly within a single tract.	Region-of-interest (ROI) approach The ROI approach allows identification between group differences in a specific brain region. Specification of the anatomical location of the putative between group differences is therefore a prerequisite. Hence, the ROI approach is often used to test findings derived from previous studies (e.g. VBA). The major problem with the ROI approach is the inability to attribute changes to a specific tract within regions containing two or more white matter bundles. Also, the manual definition of a ROI for the entire length of a tract is rarely achieved. Further, the conventional ROI approach may lack sufficient statistical power due to the high degree of intra and inter-subject variation of the fractional anisotropy values, even within a highly homogenous tract [14]. Tract-specific measurements (TSM) This approach allows testing of between group differences within a specific tract. TSM overcomes some of the limitations of the VBA and ROI analysis (e.g. better anatomical localization of the single tracts, analysis throughout the almost entire length of the bundle) but has suffered from a number of problems including operator-dependent placement of regions from which starting the tracking and difficulties in resolving the crossing or meeting of different fibres (see text).

(Table 1) [14,15•]. The method of tract-specific measurements extracts anisotropy values at regular intervals along the reconstructed fibres (Fig. 1c) [10,14,16]. Hence, tract-specific measurements can be used to assess microstructural differences within a particular tract.

In the near future the combination of DT-MRI tractography with other MRI techniques will allow specific information about the metabolic composition of the dissected tracts (e.g. diffusion tensor spectroscopy) [17], their absolute changes in T1 and T2 composition [18] and the engagement of specific tracts during cognitive tasks (for functional diffusion maps of the visual cortex see Le Bihan *et al.* [19••]) to be extracted (Fig. 1c). For example, changes in magnetic resonance spectroscopy (MRS) metabolites have been found in the white matter of patients with Alzheimer's disease and primary progressive aphasia [20]. In multiple sclerosis both MRS and T2-weighted lesions are important in establishing the diagnosis. Hence, in-vivo quantification of white matter characteristics (structural, metabolic or functional) within specific tracts represents an important step towards the identification of MRI biomarkers of disease onset and progression.

Connectional models of cognition and classical disconnection syndromes

Cerebral connections have been investigated extensively in many animal species, including monkeys, but little progress has been made in the human. This gap is frequently overlooked so that white matter pathways that have been described only in animals are cited as if they also existed in the human, 'a leap of faith that may be particularly problematic when addressing substrates of uniquely human behaviours' [1••]. Hence, one of the most important applications of DT-MRI tractography is to verify the existence of pathways described in animals and identify possible tracts that are unique to humans.

A comparative hodology has the potential of unveiling the architectural backbone of human cognition and the evolutionary changes that underlie our unique cognitive capacities. For example we have preliminary DT-MRI tractography findings suggesting some similarities between human core language networks as described with DT-MRI tractography [21••] and the connectional pattern of areas to be considered the language homologues in monkeys [22]. This supports the theory that evolution of language from monkey to human involved change in a pre-existing pattern of perisylvian connections [23]. Other tracts (e.g. the inferior fronto-occipital fasciculus) seem to be present in humans [5], but not in monkeys [24••]. Parker *et al.* [25] were the first to use DT-MRI tractography to visualize white matter tracts in both human and monkey and to address advantages and limitations of this approach. A recent comparative hodology study between human and macaque brains suggests that prefrontal cortex has similar connections in the two species, whilst the tracts projecting or originating from the ventral prefrontal cortex differ in macaques compared with humans [26•]. Similarly Ramnani *et al.* [27] showed a relatively larger prefrontal contribution to the cortico-ponto-cerebellar system in human than macaque brain.

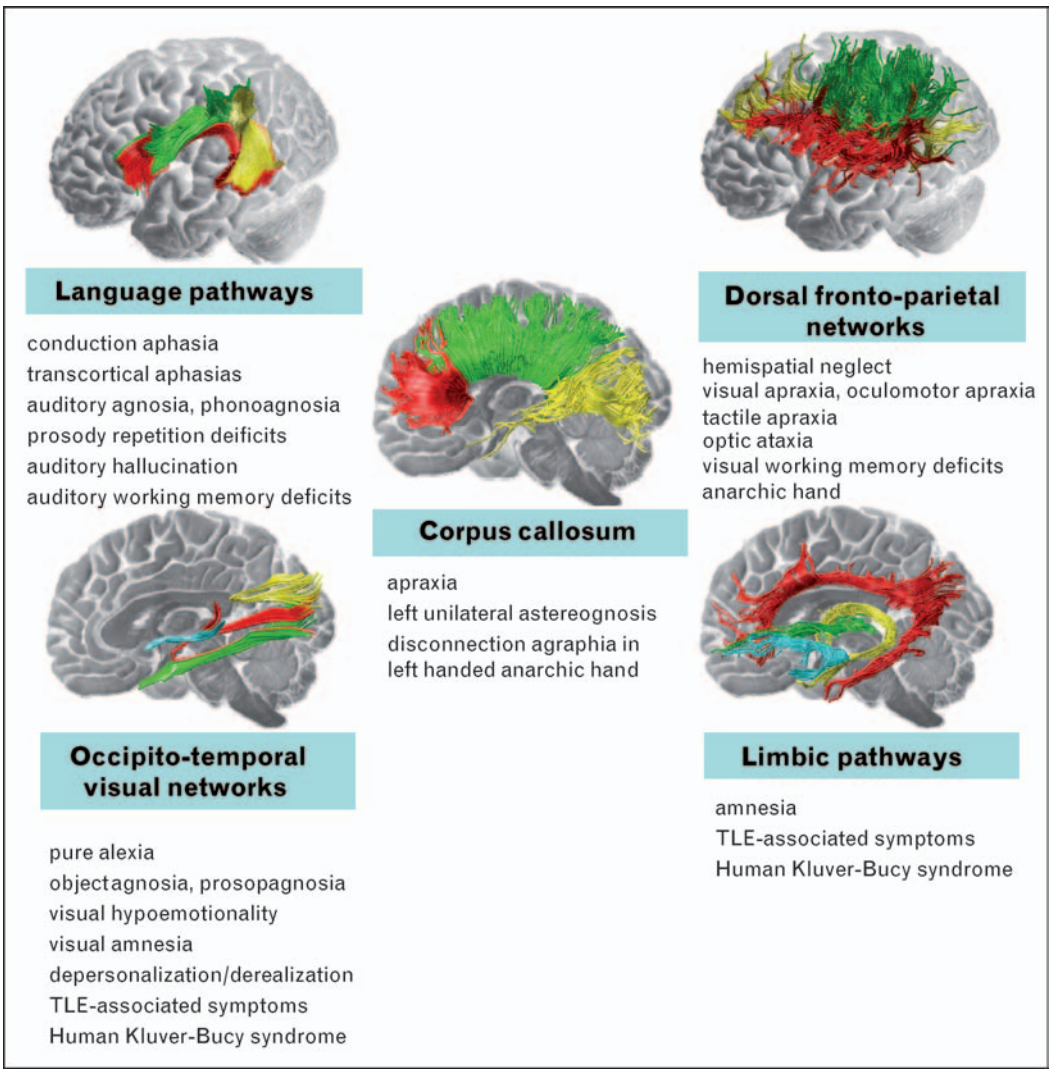
Another important application of DT-MRI tractography is to identify large-scale connectional models of higher brain functions that can be tested with other neuroimaging approaches (e.g. functional MRI) or in patient populations. Again language pathways are a good example of

such an application. Classical language networks consisted of Broca's and Wernicke's areas connected through the arcuate fasciculus. Using DT-MRI tractography a parallel pathway model for language has been described [21••]. Here a second indirect pathway runs laterally to the arcuate fasciculus connecting Broca's and Wernicke's through the inferior parietal lobe (Geschwind's territory) (Fig. 2). This arrangement not only supports the more flexible architecture of parallel processing [1••] but helps to explain why conduction aphasia, based on a disconnection between Broca's and Wernicke's areas, can have different substrates and therefore different clinical manifestations [21••].

Similarly other pathways of the human brain can be visualized with DT-MRI tractography including the dorsal parietofrontal network for spatial orientation and praxis [2•,28•], limbic network for memory and emotion [5,6,8•], callosal connections for inter-hemispheric integration [5,29], and ventral occipitotemporal networks for face and object recognition (Fig. 2) [30]. Several disconnection syndromes have been described as result of a damage to one or more tracts belonging to these networks (for reviews see Catani and ffytche [2•] and Mesulam [31]) (Fig. 2). Classical disconnection syndromes as described in the late 19th century include conduction aphasia, associative visual agnosia, apraxia, and alexia without agraphia [2•]. Other syndromes have also been attributed to a disconnection mechanism from specific sensory modality deficits (e.g. visual amnesia as first described by Ross in 1980 [32]) to complex behavioural symptoms (e.g. human Kluver–Bucy syndrome [33]). For other syndromes the disconnectionist mechanism is still debated (e.g. anarchic hand) [34]. There are a few case reports in which DT-MRI tractography has

Figure 2 In-vivo diffusion tensor magnetic resonance imaging tractography representation of large-scale cognitive networks and associated neurological and neuropsychiatric syndromes for which a disconnection mechanism has been postulated

Based on [21••] for language pathways, [2•,52•] for dorsal parietofrontal networks, [30] for occipito-temporal visual pathways and [5] for callosal and limbic pathways). Associated neurological and neuropsychiatric syndromes based on [2•,31].



been applied to visualize the disconnection mechanism, mainly in patients with lesions of the corpus callosum (see for and example Lee *et al.* [35]) or in patients undergoing brain surgery with a transient, intraoperatively induced disconnection symptom [28•].

Extending the hodological paradigm beyond classical disconnection syndromes

DT-MRI provides researchers and clinicians with a new non-invasive window into white matter changes occurring across the life span and the disconnection mechanisms operating in neurodevelopmental and neurodegenerative disorders. Most studies are at the exploratory stage, aiming to increase our understanding of the underlying disease process and defining cross-sectional differences across various subject populations.

Before reviewing data from the DT-MRI tractography literature, it is worth considering a new framework relevant for the extension of the disconnectionist paradigm beyond brain lesion patients. Historically, the term disconnection has been applied in neurology to indicate a lesion of white matter that produces a deficit of higher cognitive functions. The term hodological syndromes has been recently introduced [2•] to broaden the spectrum of disconnection mechanisms to disorders of hyperconnectivity. Hodological syndromes refer generally to a cognitive or behavioural dysfunction arising from a pathology of white matter pathways, irrespective of whether the dysfunction is one of hypoconnection, hyperconnection or a combination of the two. The term hodological syndrome avoids the use of the term 'disconnection' in those disorders for which a general connectional problem has been hypothesized (e.g. schizophrenia, autism) but there is no evidence of a white matter lesion on conventional MRI [2•].

Neurodevelopment and neurodevelopmental disorders

Normal development has been extensively studied with DT-MRI [36] and there are many ongoing DT-MRI tractography studies aimed at defining the neurodevelopmental trajectories of specific white matter tracts. A better understanding of the differential maturational processes of white matter tracts is pivotal to identifying putative aberrant neurodevelopmental trajectories of specific networks in conditions like dyslexia, autism and schizophrenia.

Klingberg *et al.* [37] used DT-MRI to study the microstructural integrity of white matter in adults with poor or normal reading ability. Subjects with reading difficulty exhibited decreased diffusion anisotropy bilaterally in temporo-parietal white matter. Also, white matter diffusion anisotropy in the temporo-parietal region of the left hemisphere was significantly correlated with reading scores within the reading-impaired adults and within the control group. The authors interpreted the decreased anisotropy as an index of disturbance of white matter structure.

DT-MRI (either using a region of interest approach, or more automated voxel-based analysis techniques) has been used to investigate white matter changes in schizophrenia, with inconsistent results [14]. Preliminary findings, from a study using tract-specific measurements within long range association frontal bundles, show that age affects fractional anisotropy values in schizophrenia patients in a different way from healthy comparison subjects [9•]. The youngest schizophrenia patients in the study sample had lower fractional anisotropy than age-matched comparison subjects, but this difference diminished with increasing age. This could be related to differences in myelination and maturational trajectories from adolescence to adulthood.

DT-MRI tractography has also been used to test a cerebellar disconnection syndrome in autism [38]. Tract specific measurements of cerebellar tracts show reduced fractional anisotropy of the local intracerebellar circuitry (e.g. parallel fibres and Purkinje tracts) and main cerebellar output but intact cerebellar afferent tracts.

Ageing and cognitive neurodegenerative disorders

DT-MRI has been used to identify age-related brain changes [39] and white matter alterations in a number of neurodegenerative disorders including Alzheimer's disease [12] and dementia with Lewy bodies (DLB) [40].

Although loss of white matter is prominent in later stages of the neurodegenerative process, preliminary DT-MRI studies in Alzheimer's disease found fractional anisotropy reduction in vulnerable white matter regions even at preclinical stages. For example DT-MRI of the corpus callosum and medial temporal lobe revealed that an increased genetic risk for developing Alzheimer disease (APOE epsilon4 carriers) is associated with reduced fractional anisotropy well before the onset of dementia [41].

In subjects with amnesic mild cognitive impairment (MCI), DT-MRI-derived measures from a left hippocampal region-of-interest demonstrate higher sensitivity (around 80%) than volume measurements of hippocampal atrophy (50%) [42•]. These changes are probably related to the underlying pathology as suggested by significant correlations between neuropsychological assessment scores and regional DT-MRI measures in MCI [43].

An even greater reduction of fractional anisotropy values is observed in vulnerable brain regions of early Alzheimer's disease patients (around 40% reduction

compared to controls versus around 30% in MCI compared to controls) [44]. Although it is most likely that reduced anisotropy within the white matter is secondary to cortical neuronal degeneration, comparative DT-MRI and postmortem pathological studies are necessary to understand the contribution of a primary white matter pathology to these changes.

Region-of-interest analysis in DLB found reduced fractional anisotropy in the corpus callosum and frontal, parietal and occipital white matter regions [40]. The authors suggest a common anatomical substrate for DLB and Parkinson's disease, which differs from the characteristic temporo-parietal involvement observed in Alzheimer's disease patients and speculate on the correlation between visuoperceptual deficits, visual hallucinations and white matter abnormalities in DLB.

DT-MRI tractography has been used to localize fractional anisotropy changes within specific networks in ageing and Alzheimer's disease. For example Sullivan *et al.* [29] used tract-specific measurements to show ageing-related reduction of fractional anisotropy within fibres of the corpus callosum. These changes correlated with performances in the Stroop task, and were more evident in the frontal portion of the corpus callosum (genu) compared to the posterior portions (e.g. splenium). In Alzheimer's disease, tract-specific measurements show fractional anisotropy changes within long range association tracts of the temporal lobe but no changes in the visual radiations [11,12].

Diffusion tensor magnetic resonance imaging in other neurological and neuropsychiatric disorders

Application of DT-MRI to explore clinico-pathological correlation of cognitive deficits in multiple sclerosis has been disappointing. Rovaris *et al.* [45] found a poor correlation between DT-MRI-derived measurements of white matter integrity and measures of cognitive impairment in patients with relapsing–remitting multiple sclerosis. Recently, the use of tract specific measurements was shown to increase the ability of DT-MRI to detect white matter pathology underlying cognitive dysfunction in multiple sclerosis [46] (in this study the integrity of the fibres of the corpus callosum was correlated with attention and information processing speed as measured by the Paced Auditory Serial Addition Test).

DT-MRI in patients with Huntington's disease suggests that alterations within cortico-subcortical connections occur both in presymptomatic individuals known to carry the genetic mutation that causes Huntington's disease and in very early in symptomatic Huntington's disease patients [47].

White matter changes are known to occur in patients infected with HIV. Wu *et al.* [48] showed that fractional anisotropy values of the splenium fibres were significantly reduced in patients infected with HIV and correlated with dementia severity and deficits in motor speed.

O'Sullivan *et al.* [49] found that white matter damage and disruption of white matter connection as measured with DT-MRI correlate with executive dysfunction in patients with ischaemic leukoaraiosis. The authors conclude that DT-MRI measurements correlate better with cognition than conventional MRI measures, and therefore may be useful in monitoring disease progression and as a surrogate marker for treatment trials.

Similarly DT-MRI measurements in normal-appearing white matter correlate with executive dysfunction in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [50].

Limitations and advantages of diffusion tensor magnetic resonance imaging tractography

An in depth discussion of the technical issues concerning DT-MRI tractography is beyond the scope of this review. Some of the advantages and limitations of the technique have been summarized in Table 2 but the reader is referred to previous works that have discussed these aspects more in detail [3,4,13].

Table 2 Diffusion tensor magnetic resonance imaging tractography

Advantages	Limitations
Hodological approach to brain function and dysfunction (versus topological localizationist approaches using Brodmann areas)	In vivo reconstruction of fibres in need of post-mortem validation (e.g. artefactual reconstructions are possible especially for projection and commissural fibres)
Allows quantitative measurements of microstructural integrity of fibres with a better anatomical localization (e.g. compared to ROI or VBA approaches, see Table 1)	Limited spatial resolution (unable to visualize bundles below 2.5 mm in diameter) and blindness to directionality (e.g. afferent or efferent fibres)
In-vivo evaluation of disconnection mechanisms beyond classical disconnection syndromes (e.g. neurodevelopmental and neurodegenerative disorders)	Requires a-priori knowledge of white matter anatomy
Useful to constrain functional connectivity models	Several pitfalls of current attempts to combine it with other brain mapping methods (e.g. tracking from activation maps)

ROI, region of interest; VBA, voxel-based analysis; fMRI, functional magnetic resonance imaging.

A major limitation of DT-MRI tractography is that the calculated trajectory of the fibre may fail to follow the true fibre tract trajectory because of the ability of trajectories to jump to adjacent structures. This is mainly due to the problem of crossing fibres [3,4] and partial volume effects [51]. The low signal-to-noise ratio of MRI limits the spatial resolution of DT-MRI tractography (with typical voxel resolutions on the order of 2.5 mm^3), which is much lower than conventional anatomical tracer methods that can establish synaptic connectivity (e.g. resolution on the micron scale) [1••,24••]. Furthermore, a major limitation of these methods is that they do not distinguish between efferent and afferent projections.

Also the regions-of-interest used as seed-points to start tracking are usually manually traced and therefore rely on a-priori anatomical knowledge. This makes DT-MRI tractography heavily operator dependent. The validity of DT-MRI tractography is harder to address, as there is no systematic accepted gold standard [4,5,24••]. Previous studies, however, showed that it is possible to obtain *in vivo* reconstruction of the major white matter tracts of the human brain, especially of the long association tracts, that are faithful to the classical post-mortem descriptions of the standard anatomical reference works [5,6].

DT-MRI tractography can also be used in conjunction with functional MRI or electroencephalography [1••,52]. Tractography-derived cortical projections can be used to constrain functional connectivity analysis. This approach can give important information about the direction of connections, or the interaction between regions within a behaviourally characterized network. Alternatively, functional MRI activation maps can be used as regions of interest from which to start tracking. The second approach is limited by several problems, including seeding from regions with higher degree of tracking uncertainty (e.g. cortical regions have lower anisotropy, therefore the orientational coherence of repeat estimates of the principal eigenvector, which indicates the main directionality of fibres, is lower in such regions) [53], limited spatial resolution of functional maps, and problems with subjects who present atypical activation maps (e.g. definition of regions-of-interest in subjects without activation of brain areas expected to engage during specific tasks).

Conclusion

In conclusion DT-MRI has shown white matter changes in a wide range of cognitive disorders. These findings were conducted in small groups and need to be confirmed in larger patient groups with better clinical characterization. All correlation analysis should be considered as exploratory and future studies are needed in which specific clinico-anatomical hypotheses are addressed, possibly by combining tract-specific measurements with cognitive testing. Although DT-MRI measurements are often interpreted as indexes of white matter integrity, it is important to remember that these measures are often confounded by a variety of technical factors.

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